English Translation of RU 2065307

Tools for treatment of primary liver cancer AND METHOD TREATMENT OF PRIMARY LIVER CANCER

Field of technology

The invention relates to medicine, more accurately,
5 Oncology, namely for the treatment of primary cancer
liver and a method for treating primary liver cancer.

PRIOR ART

Primary liver cancer is one of the most malignant
tumors of man. Treatment of patients is
1 On a difficult task. Chance of cure makes the operation
made in the early stages of disease, but more often in
neoplastic process are involved both lobes of the liver.
In addition, accompanying cirrhosis, thrombosis, and massive
infiltration of the portal vein are considered as
15 contraindications to surgery, potentially resectable
May be up to 30% of patients. Postoperative
oslazhneniya heavy, and relapse is more
Human silt than the exception. Therefore, the overwhelming number of
patients with primary liver cancer shows a conservative
20 treatment. Primary liver cancer is among the
resistant to chemotherapy of malignant forms of
neoplasms.

The effectiveness of systemic chemotherapy
Fluorouracil is extremely low, a slight improvement
results achieved by using doxorubicin.
25 Interest in regional chemotherapy continues unabated.
The introduction of cytotoxic drugs into the hepatic artery creates a
high tumor drug concentration and theoretically
should lead to an increase in therapeutic efficacy
with a decrease in overall adverse toxic reactions. More likely to
30 regional intrahepatic chemotherapy used
doxorubicin by 60-75 mg / m once in 2-6 weeks or
of 7-30 mg / m for 72 hours continuously.
The maximum life expectancy of patients treated with
effect of 20 months., combination chemotherapy
35 doxorubicin and mitomycin C did not improve results
treatment

There is a method of treatment with drugs
daunorubicin-arachidonic acid and alpha-fetoprotein
man. A method of producing these drugs is described in

Journal of Cancer Res., 43, 2668-2672 (1983). ibid
reported that the combined use of drugs
5 daunorubicin-arachidonic acid and alpha-fetoprotein
man leads to cytostatic sinergicheskoiu

Effect in in vitro experiments, when exposed to
neoplastic human cell lines that have
receptor for alpha-fetoprotein, and in experiments in
10 vivo on animals with entwined human tumors.
In 1983, Dr. Kohn was invited to use
for targeted delivery of anticancer drugs in
some types of tumor tissues hydrophobic compound
Lipiodol ultrafluid (Konno T.et al., Eur. J. Cancer Clin.
15 Oncol., 1983, 19, 1053-1065). Initially, this connection
was synthesized as a dye for
X-rays (Maeda H.et al., Eur. J.
Cancer Clin. Oncol., 1983, 9, 543-547) • Lipiodol
ultrafluid a poppy-seed oil with
2 O substituted ethyl ether, the ether of glycerol. Viscosity
compound at 15 0 to 70 senior, density at 15 0 with
-1.28. 1d.

Lipiodol ultrafLuid contains 0.38 g of iodine. At
intra-arterial injection Lipiodol ultrafLuid
disperses into small fat droplets. Because of
25 morphological differences between the capillaries of the tumor and
normal tissues of the droplets remain in the first and
quickly removed from the second (Konno T., Cancer, 1990, 66,
1897-1903). For example, in the tissues of primary liver cancer
Lipiodol ultrafluid can be up to 3 months,
3 The metastatic liver cancer, lung cancer and some
tumors of the urinary system and sex for several weeks. Of
normal tissues as shown in Lipiodol ultrafluid
average of 24 hours. This property of Dr. Cohn used
for targeted delivery of anticancer drugs in
35 tissues of primary liver cancer. Antitumor drug
previously dissolved in Lipiodol and ultrafluide
then intravenously administered to a patient. In tumor
tissue drug penetrated into rastvorennm
fat bubbles Lipiodol ultrafluid, of which
place its slow diffusion into the blood. So
way Lipiodol ultrafluid serves as a
5 reservoir of anti-cancer drug that can
maintain a relatively high concentration of the latter
long time. As further
research method allows to increase the Kono

efficacy of chemotherapy effects in
10 treatment of primary liver cancer is 2.5-3 times higher than
with the results seen with
anticancer drug in free form. as
anticancer drugs on Dr. Cohn used the
doxorubicin, mitomycin C, 5MANC5, aklarubitsin (Kopp, T.,
1S et al., Eur.J.Cancer, 1992, 28, 403-408).

Some ONKOfetalnye belkhi I in particular protein
serum alpha-fetoprotein, have a unique
property to selectively penetrate sootvetstivii with
mechanism of receptor endocytosis in some types of
20 tumor, but not normal cells (Uriel J. Et al.,
Int.J.Cancer., 1987,40, 314-318; Laborda J., Tumor Biol.,
1984, 5, 41-51). In addition to this extremely important property
AFP bind certain steroid
hormones and Pauline saturated fatty acids (Deutsh N. F.,
25 Adv.Cancer Res., 1991, 56, 253-312). Dr. Deutsch
was first formulated and then experimentally
confirmed the hypothesis about the possibility of directional
transport of anticancer drugs in some types of
tumor cells, using as
3 The transport protein alpha-fetoprotein (Deu tsh N. F.,
Adv.Cancer Res., 1991, 56, 253-312). Content of proposition
Dr. Deutsch method is as follows.
Chemically synthesized covalent complex
daunorubicin-arachidonic acid. Due to a member of the
35 composition of this complex of arachidonic acid was
able to effectively communicate with alpha-fetoprotein and
such as selectively penetrate into some of the tumor,
but not normal cells. The most effective capture
ternary complex of doxorubicin-arachidonic acid
alpha-fetoprotein place cells of hepatocellular
carcinomas (Abelev GI, Tumor. Biol., 1989,10, 63-74).
after
lost
penetration
cytostatic
tumor cell
activity in
reduced overall toxicity.
antibiotic is not
significant
priienenie doxorubicin suspezii with Lipiodol
ultrafluid with intra-arterial injection into the hepatic

10 artery leads to a significant increase (2-3 times compared with obychnyii treatments) the effectiveness of chemotherapy in the treatment of primary liver cancer.

15
20
in
a
liver,
Disclosure of invention
The present invention
the remedy for the treatment of
which would provide
laid task
primary cancer
fast high
antitumor antibiotic concentration in the tumor.
The problem is solved in that means for
growth inhibition
liver containing
As is
tumor
acting
used
primary cancer cells
substance and a carrier in
Lipiodol ultrafluid,
according to the invention, the active substance used doxorubicin-estrone, and the support of additional
25 contains the lyophilized preparation of alpha-fetoprotein man.

Although the use of Lipiodol ultrafluida known for delivery to the tumor tissues of the active substance proposed combination deksorubitsin-estrone and Lipiodol
30 ultrafluida with the addition of lyophilized preparation AFP provides not only a man
targeted delivery of doxorubicin in tumor-estrone, but not normal cells, but also provide high concentration of antitumor antibiotic in opuh.olevyh
35 tissues, which can significantly improve effectiveness of treatment for primary liver cancer. Doxorubicin-estrone can be obtained as described in.

RU, A, N 2026687.
The complex of doxorubicin-estrone is a
dark-red crystalline powder formula C49H47015N
molecular weight of 895.96 and the following chemical
structure: OH
N.3SH OH ·
I
...
About
11
with ..... OH
'OH
H "c ~
but NH O
r 11
o = c ~ c-
- The most expedient to use the following
the ratio of active ingredient and the carrier with the addition of:
solution of doxorubicin-estrone in 96% ethanol in
amount of 20-60 mg 10-15 ml Lipiodol and ultrafluida
20 2-10 mg protein of human alpha-ml saline at 12-15,
It is helpful to use a solution doksorubitsinekstrona
when heated to 70-76 0 C ethanol.

According to the invention for the treatment of primary
liver cancer, may be a separate set of
25 tightly packed products, and include
sterile doxorubicin-estrone in the amount of 20-60 mg,
Lipiodol ultrafluid of 10-15 mg aLfafetoprotein
in the amount of 1-10 mg.
We have developed a method of treating spetsialno primary
3 The liver cancer, which includes preparation of the solution
active ingredient in Lipiodol ultrafluide and introduction
this solution into the hepatic artery, with a
active substance use 20-60 ml doksorubitsinestron
And it was dissolved in 96% ethanol, heated
35 to 70-76 0 C was added n ~ piodol ultrafluida in the number of
10-15 ml, for 10-30 minutes prior to the introduction of this solution
injected into the hepatic artery in alpha-fetoprotein
number of 2-10 mg in 12-15 yl of saline solution.
Such a method can significantly reduce the side-
toxic effects, increase the effectiveness of chemotherapy
impact and reduce the dose of anticancer
5 doksoru5itsin substance-estrone compared with the applicable
at present doses of doxorubicin.

Luchshenie EMBODIMENTS
The patient is prepared for the procedure as an ordinary
angiographic study. After percutaneous Catete-
10 the polarization of the aorta distal end of the Seldinger catheter
installed in the hepatic artery (common or
proper hepatic), performed with angiography
subsequent analysis of the arterial and venous phases. Under
X-ray television control with the help of X-ray
15 contrast agent (verografln, triomtrast) should be
see places without shunt in the other, except
hepatic system, vascular pools. Freeze-dried
sterile preparation of alpha-fetoprotein is introduced
intravenously in an amount of 2-10 mg in 12-15 ml
20 saline solution. After 20 minutes, provided
lack of immediate adverse toxic effects
(Allergic reactions, chest pain, fall
blood pressure, tachycardia, tachyarrhythmia)
sterile set of Doxorubicin-estrone in the number of 20 -
25 60 mg dissolved in 0,5-1.5 ml of 96% ethanol at
heated to 70-7B Hos. The resulting solution was transferred to a 10 -
15 sludge pre-warmed Lipiodol ultrafluida.
The resulting slurry is cooled to 32-37 0 C and injected under
rentgenotelevideniya control into the hepatic artery.
30 After 3-4 weeks to repeat the administration of drugs
alpha-fetoprotein and a range of doxorubicin-estrone on
described above.

Total proposed method were treated with 10
patients aged 21 to 65 years old male and female
35 floor. Conditions of pre-selecting patients were as follows:
absence of jaundice and ascites, inoperable, no
severe concomitant diseases. Assessment of toxicity and
effectiveness was conducted by kriteriyam_VOZ. have been studied
parahetry following after treatment: duration
sequence of remission at the time of treatment to Chala
progression in the evaluation of treatment .. stabilization
5 zatsiya, "" minimal, "" partial, "" full effect "and
tahzhe life expectancy of patients who
were calculated from the start of treatment. In the treatment of patients
assigned to the following survey: graiia coagulation,
ECG, clinical blood and urine tests, laparoscopy,
10
15
oprelelenie levels of AFP, angiography,
computed tomography, ultrasound tomography.

Key findings are presented in Table 1.

Table 1.
duration
life (months)
20 Control
25
1
2
3
4
5
6
6
8
5
12
6
7
6
8
5
6
7
Patients poluchavmie alpha-fetoprotein and
30 doxorubicin-estrone
35
40
1
2
3
4
5
6
7
8
9
110
12
16
14
13
16
14
13

17
14
15
13
17
Note: The control patients were, patients with primary
liver cancer who underwent conventional
45 course chemotherapy of doxorubicin (6 O -75 mg / square meters.
once in 2-6 weeks or 7-30 mg / m². for
72 hours continuously).

Example 1.
8
Excerpt from the case 126/98.
Patient BG : Primary liver cancer.
PCGIRU9S/00030
5 conducted a chemotherapy course is
an intra vvedenenie alpha-fetoprotein in
amount of 4 mg of the drug doxorubicin-estrone in
50 mg with repeated injections after 3 weeks.
As a result, the level of alpha-fetoprotein levels decreased
10 to 56 mg / ml (a measure of pre-treatment) to 10 ng / ml after 15
months after treatment. The result was a treat
significant improvement of biochemical exponents of blood
reduction in tumor size was achieved long
bolezni.kv remission.
once in 2-6 weeks or 7-30 mg / m². for
Conclusion: The proposed course of chemotherapy contributes to
20
25
blaropriyatnomu course of the disease. continue treatment
under the proposed scheme in case of relapse
disease. The patient was observed for 17 months. The final ~ d
diagnosis: Long-term remission of the disease, metastases
otsuststvuyut
Survey) •

Example 2.
(According to
Excerpt from the case 123/57.
Patient LD : Primary liver cancer.
tomographic
The above course is a chemotherapeutic
an intra vvedenenie alpha-fetoprotein in
amount of 6 mg and the drug doxorubicin-estrone in
the 60-mg injections with repeated after 4 weeks.

As a result, the level of alpha-fetoprotein levels decreased
30 102 mcg / ml (a measure of pre-treatment) to 8 ng / ml after 16
months after treatment. The result was a treat
significant improvement of biochemical exponents of blood
disappearance
disease.
achieved prolonged remission

35 Conclusion: The proposed course of chemotherapy contributes to
favorable course of the disease. Continue treatment
under the proposed scheme in case of relapse
disease. The patient was observed 20 months. final
diagnosis: Long-term remission of the disease, metastases
otsuststvuyut, the tumor is not detected (according to
tomographic examination).
Thus, the proposed method can significantly
improve ways to treat cancer
diseases.
For the treatment of primary liver cancer may
be a set that includes: sterile
10 lyophilized preparation of human alpha-fetoprotein in
number of 1-10 mg in bottles with a capacity of 10 ml
sterile drug doxorubicin-estrone in the number of 20 -
60 mg vials with a capacity of 15 ml, sterile
saline 15 ml in an ampoule, 96%
15 ethanol 5 ml in an ampoule, sterile Lipiodol
ulotrafluid 20 ml in two 10 ml ampoules.
Set is used as described above, ie
pre-exercise hepatic catheterization
artery. Rengenotelevizionnym under control with the help
20-RENGO contrast medium in the absence of sure
25
shunt in the other, except for hepatic system,
vascular pools. Lyophilized sterile alfafetoprotein
administered intravenously in an amount of 2-10 mg
in 12 ml of saline. After 2 min at About
the absence of adverse toxic effects
sterile substance doxorubicin-estrone in the number of 20 -
About 6 mg is dissolved in O, 5-1, 5 ml of 96% ethanol at
heated to 70-76 0 with. The resulting solution was transferred to a 10 -
15 ml pre-warmed Lipiodol ultrafluid.
30 The resulting suspension was cooled to z7Ds and injected under
rentgenotelevideniya control into the hepatic artery.
After 3-4 weeks of conducting reintroduction aLfafetoproteina
and substance doxorubicin-estrone as described
above procedure. The ratio of alpha-fetoprotein and

35 agents doxorubicin-Lipiodol solution of estrone in
ultrafluid in the body for the occasional injection of the drug
is / mg / 10.2: 20-60, respectively.
Promymlennaya applicability
The proposed treatment for primary liver cancer
and method of treatment with this medication have been
used in clinics in Russia and gave a positive
5 results.

CLAIMS
1 • A tool for the suppression of tumor cell growth
primary liver cancer, which contains the active substance and
carrier, which is used as Lipiodol
5 ultrafluid, characterized in that as
active ingredient used doxorubicin estrone, and
carrier further comprises freeze-dried
preparation of human alpha-fetoprotein.

2. The tool of claim 1, characterized in that the use
10 solution of doxorubicin in 96% ethanol in an amount
20-60 mg in 10-15 ml Lipiodol ultrafluida and 2-10 mg
alpha protein in human cells 12-15 saline.

3. The tool of claim 2, characterized in that the use
solution of estrone in the doxorubicin-heated to 70-76 0 C
15 etilovok alcohol.
20
25

4. For the treatment of primary liver cancer,
represents a set of separately
packed
includes
number
drugs, wherein
a sterile doxorubicin
20-60 kg, Lipiodol in ultrafLuid
hermetically
that the set
estrone in
number
10-15 kg, alpha-fetoprotein in the amount of 1.10 u.

5. The tool of claim 4, characterized in that it contains
Saks known for his saline solution consisting of 15 cells and

96% ethanol at 5 cl.

6. A method for treating primary liver cancer, including
preparing a solution of the active substance in
Lipiodol ultrafluide and the introduction of this solution
hepatic artery, featuring a tech, that as
active substance use 20-60 cells, doxorubicin
30 estrone and dissolve it in 96% ethanol, heated
to 70-76 0 C, was added in the amount of Lipiodol ultrafluida
35
10-15 cells, for 10-30 minutes prior to the introduction of this solution
injected into the hepatic artery in alpha-fetoprotein
number of 2-10 mg in 12-15 ml of saline solution.

7. The method according to claim 6, characterized in that described in
p.6 way to repeat the treatment after 3-4 weeks.